Psychosis-associated DNA methylomic variation in Alzheimer's disease cortex

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HIGHLIGHTS

- Psychosis is common in AD and has a negative impact on the course of the disease.
- We compared genome-wide DNA methylation in AD donors with and without psychosis
- The top ranked genes were enriched for known schizophrenia GWAS and EWAS loci
- We observed two significant differentially methylated regions with multiple CpGs
- AD+P-associated methylation of *AS3MT* gene was replicated by pyrosequencing

ABSTRACT

Psychotic symptoms are a common and debilitating feature of Alzheimer's disease, associated with a more rapid course of decline. Current evidence from post-mortem and neuroimaging studies implicates frontal, temporal and parietal lobes, with reported disruptions in monoaminergic pathways. However, the molecular mechanisms underlying this remain unclear. In the present study, we investigated methylomic variation associated with AD psychosis in three key brain regions implicated in the etiology of psychosis (prefrontal cortex, entorhinal cortex and superior temporal gyrus) in post-mortem brain samples from 29 AD donors with psychosis and 18 matched AD donors without psychosis. We identified psychosis-associated methylomic changes in a number of loci, with these genes being enriched in known schizophrenia-associated genetic and epigenetic variants. One of these known loci resided in the *AS3MT* gene – previously implicated in schizophrenia in a large GWAS meta-analysis. We used bisulfite-pyrosequencing to confirm hypomethylation across four neighboring CpG sites in the *ASM3T* gene. Finally, our regional analysis nominated multiple CpG sites in *TBX15* and *WT1*, which are genes that have been previously implicated in AD. Thus one potential implication from our study is whether psychosis-associated variation drives reported associations in AD case-control studies.

Keywords: Alzheimer's disease, brain, DNA methylation, epigenetics, psychosis, schizophrenia

1. INTRODUCTION

Around 40% of people with Alzheimer's disease (AD) will at some point experience psychotic symptoms, which are distressing, have a major negative impact on disease course and accelerate the need for nursing home care (Connors, et al., 2018) and for which there are no effective licensed treatments (Creese, et al., 2018). The limited knowledge of disease mechanisms underlying psychosis in AD (AD+P) represents a major obstacle in the identification of novel treatment targets and understanding the syndrome at a clinical level. Neuropathological studies implicate increased pTau and TDP-43 pathology in the pathogenesis of AD+P (Murray, et al., 2014). The heritability of AD+P is estimated to be 61% (Bacanu, et al., 2005) and linkage studies (Hollingworth, et al., 2007) and population level analyses of common single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) provide further support for a genetic basis to the syndrome (Barral, et al., 2015, Hollingworth, et al., 2007, Zheng, et al., 2015). Interestingly, some of these studies suggest genetic links with schizophrenia (SZ) (Creese, et al., 2019, DeMichele-Sweet, et al., 2018), thus raising the question as to whether there are common mechanisms that underpin psychosis across the lifespan. These genomic and neuropathological studies provide compelling evidence that AD+P represent a syndrome of AD with a distinct neurobiological profile, potentially offering exciting opportunities for precision medicine. However, neuropathology explains only ~18% of AD+P variance (Krivinko, et al., 2018), while the genomics of other complex disorders suggest that common SNPs alone are likely to only explain a small proportion of variance (Golan, et al., 2014). Therefore, further research is required to provide a better understanding of the molecular mechanisms underlying AD+P, and whether this presents novel precision treatment opportunities.

In recent years, epigenome-wide association studies (EWAS) have transformed our understanding of the molecular aetiology of AD (Lunnon, et al., 2014, Smith, et al., 2019, Smith, et al., 2018) and psychiatric conditions, including SZ (Viana, et al., 2017). Here, we present the first EWAS of AD+P in cortical samples from pathologically confirmed AD cases that had undergone a standardized assessment of psychotic symptoms during life, hypothesizing that alterations in DNA methylation are associated with AD+P.

2. MATERIALS AND METHODS

2.1. Sample selection

This study used DNA methylomic data previously generated by our group using post-mortem human brain tissue from the MRC London Neurodegenerative Disease Brain Bank (LNDBB) using the Illumina Infinium HumanMethylation450K BeadChip (Lunnon, et al., 2014) (GEO accession number GSE59685). Data from a total of 141 matched cortical samples from the entorhinal cortex (EC), prefrontal cortex (PFC) and superior

temporal gyrus (STG) were used from 29 AD+P subjects and 18 AD subjects without psychosis (AD-P) (**Supplementary Table 1)**. Samples and clinical data were collected as part of the Alzheimer's Research UK funded study "Biomarkers of AD Neurodegeneration", participants were recruited through secondary care in England with informed consent provided according to the Declaration of Helsinki (1991). During life, all cases received a clinical diagnosis of dementia. At post-mortem, all cases underwent a thorough standardized examination and all cases in the present analysis were diagnosed with AD post-mortem. There was no significant difference in the distribution of neurofibrillary tangle (NFT) Braak stage between the AD-P and AD+P groups. The following comorbid pathologies were present in the cohort but numbers (provided in Supplementary Table 1) were not significantly different across AD+P and AD-P groups: TDP-43, cerebral amyloid angiopathy (CAA), vascular pathology (including small vessel disease), Lewy body pathology (brain stem or limbic predominant). There were no cases with cortical Lewy body disease. Psychosis was assessed using the Neuropsychiatric Inventory (NPI), a ten-item scale measuring a range of neuropsychiatric symptoms reported in dementia (Cummings, et al., 1994). Assessment with NPI was undertaken at baseline and average mini-mental state examination (MMSE) at the time of assessment was 12.7 (SD=9). For this analysis, symptoms were coded as present (>0 on either the delusion or hallucination items of the NPI) or absent (no symptoms).

2.2 Illumina 450K array data analysis

The raw signal intensities for the arrays were imported into R (version 3.6). Stringent quality-control and normalization were performed separately for each region using wateRmelon and methylumi packages in R as described previously (Lunnon, et al., 2014). The minfi package in R was used to estimate the proportion of neuronal cells across samples for each tissue (Aryee, et al., 2014). The effects of age, sex and derived neuronal cell proportion were regressed out from the normalized methylation beta values for all samples before subsequent analysis. Principal component analysis demonstrated that variables such as post-mortem interval (PMI) and batch did not impact on the data and so these were not included as co-variates. Global analysis of DNA methylation data was estimated by the cumulative distribution function (CDF) of the methylation values for each individual using B-spline basis functions using the GAMP package in R (v.0.11) (Zhao, et al., 2015). The estimated global DNA methylation levels in the AD+P and AD-P groups were compared in each of the cortical brain regions. In order to identify differentially methylated positions (DMPs) consistently associated with AD+P across all three cortical regions, we performed a linear model analysis using generalized least squares ('gls' function in nlme R package (Pinheiro, et al., 2019), which allows for a

fully unstructured variance-covariance matrix of the residuals. Fixed effects were specified in such a way that we directly obtained the pooled estimate and standard error (SE) across the brain regions. Quantile-quantile (Q-Q) plots were used to assess the inflation index (**Supplementary Fig 1**). DMPs were ranked by both P-value and the magnitude of effect size. To identify differentially methylated regions (DMRs), we used the Python module comb-p to group ≥3 spatially correlated *P*-values in a 500-bp sliding window (Pedersen, et al., 2012). To test for an enrichment of the AD+P EWAS loci in known SZ GWAS variants we used Fisher's method to combine together AD+P EWAS P-values for probes residing in the independent genome-wide significantly associated regions nominated in the most recent SZ GWAS meta-analysis (Pardinas, et al., 2018). Of the 145 regions identified by Pardinas and colleagues, 101 contained > 1 CpG site on the 450K array and were used in our analyses. Finally, to test for an enrichment of the AD+P EWAS loci in known SZ EWAS variants we used a one-sided Fisher's test to test whether the 1,000 top-ranked AD+P-associated probes in our EWAS were enriched in a list of 1,894 significant SZ-associated probes (P_{FDR}< 0.05) from a recent SZ EWAS of PFC (Jaffe, et al., 2016).

2.3 Targeted validation using bisulfite-pyrosequencing

Bisulfite pyrosequencing was used to replicate DNA methylation in the same samples and tissues across six individual CpG sites in the *AS3MT* gene, spanning from chr10:104629829-104629929 (hg19). Bisulfite conversion was performed using the EZ DNA Methylation-Gold kit (Zymo Research, USA). A single amplicon (101 bp) was generated using primers designed using the PyroMark Assay Design software 2.0 (Qiagen, UK). Pyrosequencing was performed using two sequencing primers to maximize coverage across the five CpG sites. DNA methylation was quantified using the Pyromark Q24 system (Qiagen, UK) using the manufacturer's standard instructions and the Pyro Q24 CpG 2.0.6 software. To examine the combined effect of the CpGs across the designed amplicon for pyrosequencing, the measured DNA methylation for each site was tested using the generalised least square (GLS) method and estimates and corresponding variance-covariance matrix of the estimates were subjected to the 'rma' function in the metafor R package (v2.1) (Viechtbauer, 2010).

3. RESULTS AND DISCUSSION

3.1. *AD+P is characterised by common patterns of methylation across brain regions*

The aim this study was to identify distinct patterns of DNA methylation associated with the presence of psychosis in AD. Therefore, we performed an EWAS in the 29 AD+P and 18 AD-P samples, whilst controlling for confounders such as age, sex and derived neuronal cell proportions. First, we used the cumulative

distribution function (CDF) of the methylation values for each individual to quantify global methylation levels across samples and observed no difference in global DNA methylation between AD+P and AD-P individuals in any of the three brain regions examined (PFC: P=0.99, EC: P=0.52, STG: P=0.76). Next, we examined DNA methylation differences between AD+P and AD-P subjects at individual loci covered by the array, with the 1,000 top-ranked loci (based on both effect size and P value) shown in **Supplementary Table 2**. Although no CpGs survived the stringent Bonferroni significance threshold of *P*<1.66E-07, a number of loci showed similar patterns of methylation across all three brain regions. Interestingly, the top ranked probe (cg19596870, estimate= -0.173, *P*=3.42E-04) and the 11th ranked probe (cg01266060, estimate= -0.029, *P*= 3.00E-05) reside within the *SERPINB6* gene, located 498bp downstream from the TSS and in the gene body, respectively. This gene is expressed in the brain and has been previously identified in a SZ-coagulation gene interaction network (Huang, et al., 2014). We also identified DMPs annotated to other genes that have previously been implicated in SZ; our 76th ranked loci resided within the body of the *AS3MT* gene (cg08772003, Estimate= -0.025, P= 7.50E-04), where increased gene expression has been linked to SZ risk alleles in the 10q24.32 SZ-related locus.

3.2 A number of DMRs spanning multiple adjacent CpGs are seen in AD+P

We identified two DMRs, each with consistent hypomethylation in the AD+P group in all three cortical regions (**Supplementary Table 3**). These regions corresponded to ten CpG sites (613bp) within the first exon of the *TBX15* gene (**Fig 1A**: P_{Sidak}= 5.88E-09) and eight CpG sites (476bp) in the first intron of the *WT1* gene (**Fig 1B**: P_{Sidak}= 3.00E-08).

3.3 Differentially methylated loci in AD+P are enriched for known SZ variants

Given that several of our top-ranked DMPs appeared to have been previously associated with SZ, we were interested whether there was a significant enrichment of significant DMPs within known SZ-associated variants. To this end, using the most recent list of independent SZ-associated genomic regions from Pardinas *et al* (Pardinas, et al., 2018), we examined the enrichment of AD+P-associated DMPs residing in the linkage disequilibrium (LD) blocks harboring risk variants. 101 of the 145 LD blocks contained > 1 CpG site on the 450K array and using Fisher's method we combined P-values within each of these blocks, identifying a significant enrichment in our data in locus 1 after correcting for multiple testing (Chr6: 24988105-33842877; xMHC (10,409 probes), P_{FDR} = 1.21E-04) (**Supplementary Table 4**). Notably, we observed that 40 of the genes annotated to our 1,000 top ranked AD+P probes were in the significant SZ EWAS probe list with the same direction of effect, including *TBX15*. When we correlated the t-statistics of our EWAS with the SZ EWAS

for these 40 CpG sites we observed a highly significant correlation (r = 0.87, p = 2.672E-13). Finally, we found 19 of the genes we identified in our AD+P EWAS were present in the list of 376 differentially expressed genes (at FDR) in the recent meta-analysis of transcriptomic data in SZ by Manchia and colleagues (Manchia, et al., 2017), demonstrating a significant enrichment (P = 0.035).

3.4 Bisulfite pyrosequencing replicates hypomethylation of the AS3MT gene in cortex

We used bisulfite pyrosequencing to quantify DNA methylation across an extended region of 101bp spanning five CpG sites, including cg08772003, one of the top-ranked DMPs we had identified within the exonic region of *AS3MT*. This gene was selected for validation given its reported role in the pathogenesis of SZ (Li, et al., 2016). In our 450K analysis we had observed hypomethylation in AD+P at cg08772003 in all three cortical regions (**Fig 2A**). Using pyrosequencing we observed a trend towards significant hypomethylation across the three regions (**Fig 2B**), with DNA methylation values calculated on the 450K array being highly correlated with the values calculated by pyrosequencing (**Fig 2C**). Our pyrosequencing assay covered four additional CpG sites, three of which were downstream of cg08772003 (**Supplementary Table 5**). Interestingly, these three CpGs all showed the same direction of effect as the CpG covered by the 450K probe (hypomethylation) (**Fig 2D-E**), and when we averaged methylation across the four hypomethylated sites these showed significant hypomethylation (*P* =0.0011) associated with AD+P.

5. CONCLUSIONS

We examined cross-cortical DNA methylation changes associated with AD+P in a series of clinically and neuropsychological well-characterized cases. We found consistent patterns of DNA methylation across entorhinal, temporal and frontal cortex, with the top ranked loci being enriched for known EWAS and GWAS SZ loci. To our knowledge, this is the first evidence implicating DNA methylation in AD+P and adds further support for transdiagnostic hypotheses linking psychotic disorders across the lifespan.

We identified DMRs in *TBX15* and *WT1*, which were hypomethylated in AD+P relative to AD-P. It is interesting to note that these genes have been previously reported in the context of AD; *TBX15* has been shown to be hypomethylated in in the superior temporal gyrus of AD cases relatives to non-AD controls (Watson, et al., 2016), whilst *WT1* has been previously shown to be present in neurofibrillary tangles (Lovell, et al., 2003). Although our findings should be replicated in independent cohorts, one potential important broader implication from our study is whether AD+P-associated variation drives reported genetic, epigenetic or transcriptomic associations previously identified between AD cases and non-AD controls. Given that

around ~40% of AD patients will experience psychosis (Connors, et al., 2018), which is seldom measured or reported, it is plausible that psychosis could represent a significant confounder in AD case-control studies, which cannot easily be accounted for.

There are several converging lines of evidence to suggest that psychotic symptoms across the lifespan have some common mechanisms. Recent genomic research has linked polygenic risk for SZ to psychotic symptoms in Huntington's disease (Ellis, et al., 2019) and AD (Creese, et al., 2019), as well as psychotic experiences in the general population (Legge, et al., 2019), while neuropsychological testing implicates similar deficits in processing speed and executive function in individuals with very late onset SZ-like psychosis and AD+P (Van Assche, et al., 2019). Our findings that top-ranked AD+P-associated DMPs are enriched for SZ loci extends this evidence base into molecular-level mechanistic similarities for the first time

We are unable at present to determine whether the AD+P-associated DNA methylation patterns we have identified are causal or a consequence of the psychotic episodes. Nonetheless, given that many of the top ranked loci overlapped with known psychosis-associated genetic variants, it does suggest that some of the epigenetic variation we have identified may lie upstream of symptom onset. There are a number of other limitations to our study, for example the use of bulk tissue, which contains both glia and neuronal cell types and our relatively small sample size in this study. Although we were able to validate AD+P-associated hypomethylation in the *AS3MT* gene using another technology, this was on the same samples and thus it will be important in the future to validate our findings in additional similarly well-characterised cohorts. Nonetheless, the quality of clinical and neuropathological phenotyping is a key strength of our study and our findings provide a clear rationale for further molecular level profiling of AD+P.

DISCLOSURE

All the authors declare that they have no conflicts of interest with this work.

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Figure 1: Two DMRs consisting of multiple adjacent DMPs can be identified in AD+P. (**A**) Ten DMPs showed hypomethylation in *TBX15* and (**B**) eight DMPs in *WT1* showed hypomethylation in AD+P (red) compared to AD-P (orange) in all three cortical brain regions. Shown on the X axis is genomic location. Shown on the Y axis is the corrected DNA methylation level (%).

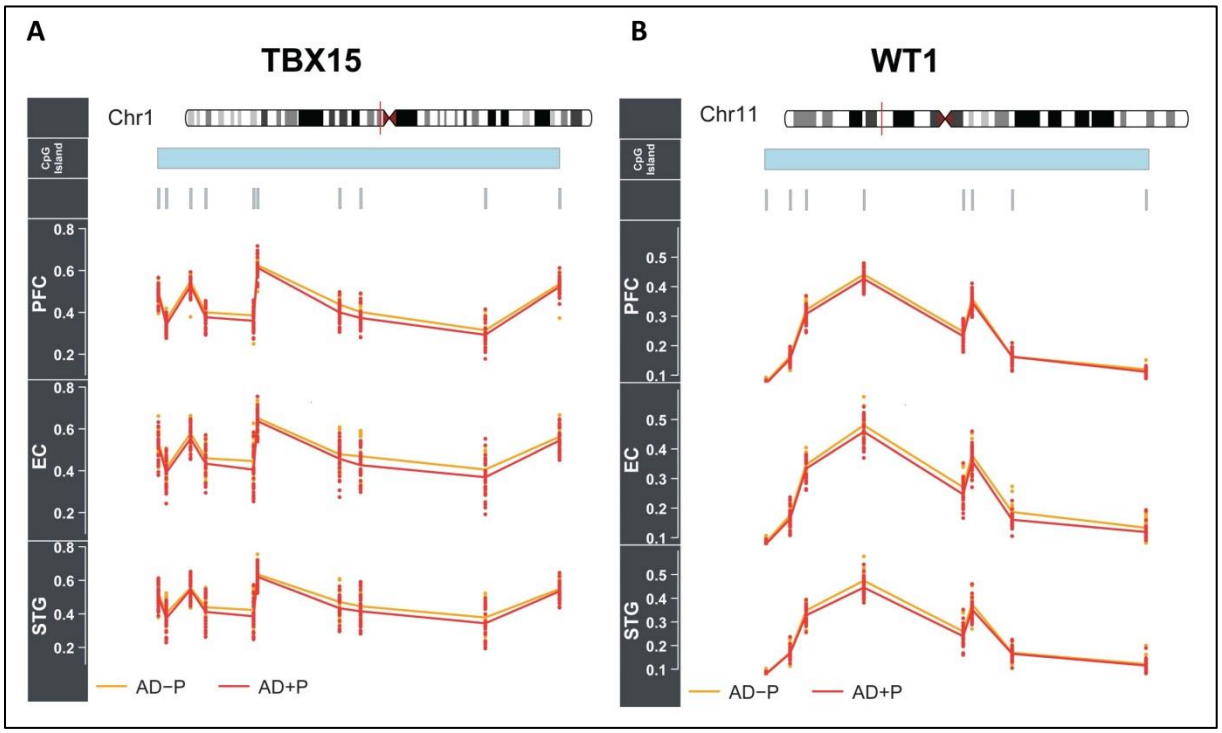
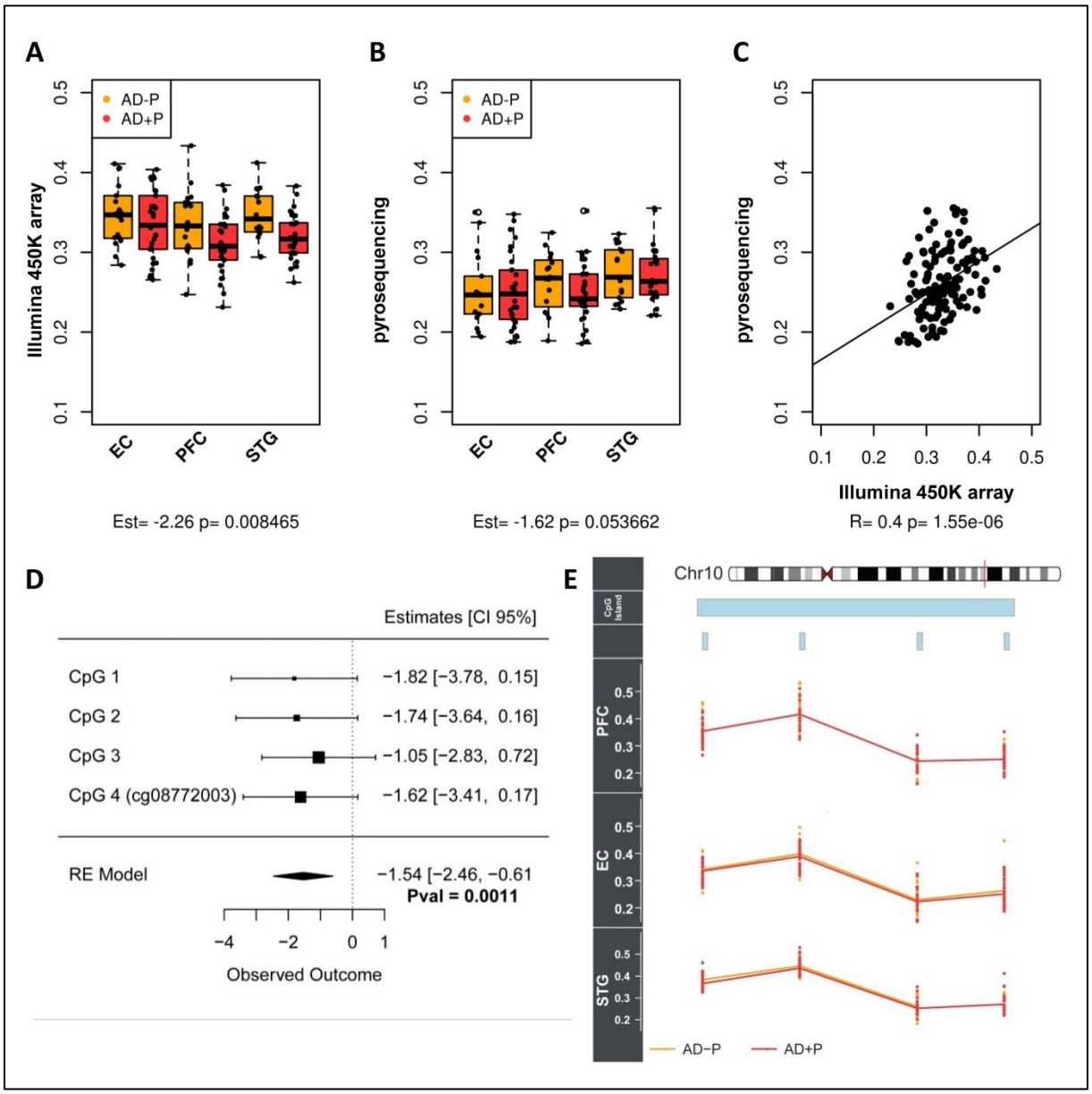
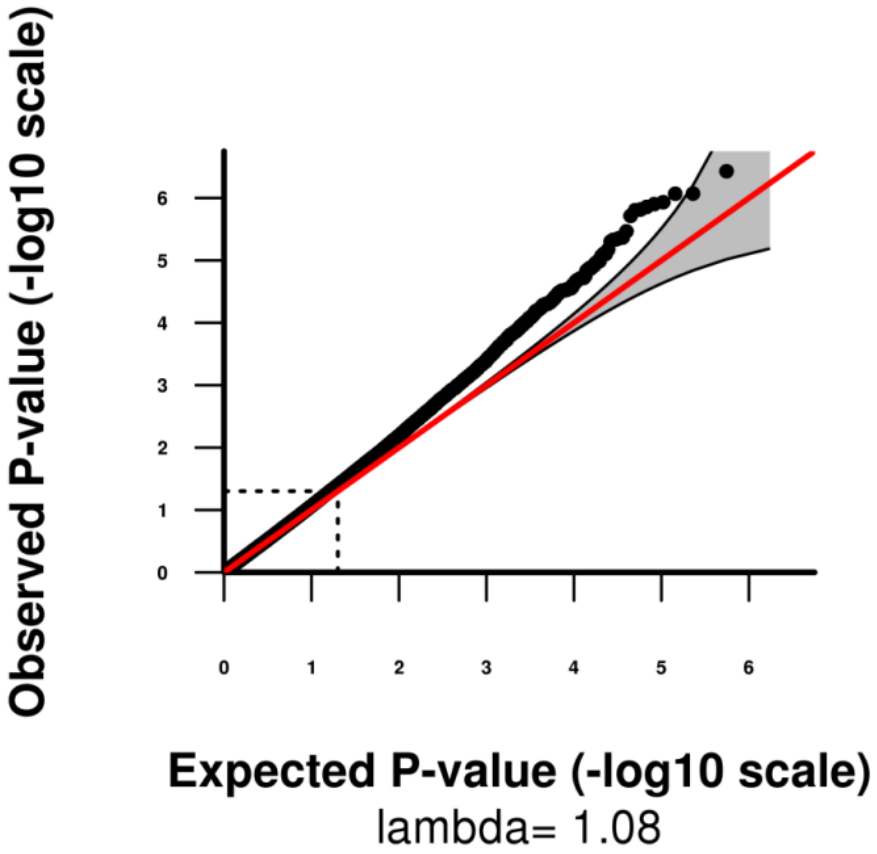


Figure 2: *AS3MT* shows consistent hypomethylation in AD+P using two different technologies. In the 450K array data we demonstrated significant AD+P-associated hypomethylation across all three cortical brain regions at cg08772003 (**A**), with a similar trend at this loci when replicated using pyrosequencing (**B**) and a significant correlation of methylation levels calculated by the two technologies (**C**). Three neighboring downstream CpG sites covered by the pyrosequencing assay also showed psychosis-associated hypomethylation across the cortex, which was significant across the region (**D**, **E**).



Supplementary Figure 1: A QQ plot of expected versus observed *P* values in the AD+P EWAS.



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